UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Date: **January 29, 1998**

MEMORANDUM

SUBJECT: ***PIRIMIPHOS-METHYL*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland 1/29/98
Executive Secretary,
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: K. Clark Swentzel, Chairman, K. Clark Swentzel 1/27/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Mike Metzger, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Alberto Protzel, Branch Senior Scientist
Toxicology Branch 1
Health Effects Division (7509C)

PC Code:/08102

On January 12, 1998, the Health Effects Division's Hazard Identification Assessment Review committee evaluated the toxicology data base of Pirimiphos-methyl and selected doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments, re-assessed the Reference Dose (RfD) established for chronic dietary risk assessment and addressed the sensitivity of infants and children as required by the food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were Karl Baetcke, William Burnam, Susan Makris, Nancy McCarroll, Mike Metzger, Kathy Raffaele, Jess Rowland (Executive Secretary) and Clark Swentzel (Chairman). Member in absentia: George Ghali, Karen Hamernik, and Melba Morrow. Other HED staff participating were William Sette, Science Analysis Branch and Christina Swartz, Reregistration Action Branch 2. Data was presented by Sanju Diwan of Toxicology Branch 1.

Data Presentation: Sanju Diwan

Sanju Diwan, Ph. D
Toxicologist

Report Preparation: _____

Jess Rowland, M.S
Executive Secretary

I. INTRODUCTION

On January 12, 1998, the Health Effects Division's Hazard Identification Assessment Review committee evaluated the toxicology data base, selected doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments, re-assessed the Reference Dose (RfD) established for chronic dietary risk assessment, and addressed the sensitivity of infants and children from exposure to Pirimiphos-methyl as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented below.

II. HAZARD IDENTIFICATION

A. Acute Dietary (one-day)

Study Selected: 28-Day and 58-DayOral Toxicity - Human

MRID. Nos. 00097671 and 00080732

Executive Summaries: In the 28-day study, 5 healthy adult human **males** received gelatin capsules containing Pirimiphos-methyl (97.8%) at a dose of 0.25 mg/kg for 28 days. Plasma and erythrocyte cholinesterase activities (ChEI) were measured twice prior to dosing, on days 1, 2, 3, 7, 14, 21 and 28 of dosing as well as on days 7 and 14 post-dosing. **No biologically significant effects were seen on plasma or erythrocyte ChEI during days 1 through 7**. One subject showed borderline depression of plasma ChEI on days 14 and 28 (-13% and -21%, respectively below predosing measurement).

In the 56-day study, 3 healthy adult human **males** and 4 **females** received Pirimiphos-methyl(97.8%) at the same dose (0.25 mg/kg) for 56 days. Plasma and erythrocyte cholinesterase activities (ChEI) were measured twice prior to dosing, on days 1, 7, 14, 21, 28, 35, 42, 49 and 56 of dosing as well as on days 7, 14, 21 and 28 post-dosing. **No biologically significant effects were seen on plasma or erythrocyte ChEI during days 1 through 3**. Statistically significant decreases in plasma ChEI (up to 24%, relative to lowest and/or mean pre-dosing activity) were seen in 3 females between days 14 and 35.

Dose and Endpoint for Risk Assessment: NOEL = 0.25 mg/kg/day based on lack of cholinesterase inhibition up to day 7.

Comments about Study and Endpoint: This dose was considered to be the NOEL for acute effects (i.e., after a single exposure) since ChEI was not observed in either study until day 14. In addition, Although no plasma or erythrocyte ChEI was seen in either study, the Committee selected this dose since it was the only dose that was tested and it was presumed that a higher dose could have caused ChEI.

This risk assessment is required.

Acute Dietary Risk Assessment: Although, the developmental toxicity studies in rats and rabbits showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures and the two-generation reproduction toxicity study in rats showed no increased sensitivity in pups when compared to adults, the Committee determined that **the FQPA 10 x factor should be retained** because of the inadequate data base 1) to evaluate acute delayed neurotoxicity following a single exposure, 2) to assess the functional development of young animals and in turn the susceptibility to infants and children and 3) to determine the need for a developmental neurotoxicity study. The data gaps are listed in Section VI.

Thus, for acute dietary risk assessment, **a Margin of Exposure (MOE) of 100 is required.** This 100 includes the conventional 10 x (for use of a human study) and a 10 x under FQPA.

B. Chronic Dietary [Reference Dose (RfD)]

The RfD established in 1988 was re-assessed by this Committee pursuant to the FQPA and is discussed below:

Study Selected: 56-Day Oral Toxicity - Human

MRID No. 00080732

Executive Summary: In the 56-day study, 3 healthy adult human **males** and 4 **females** received gelatin capsules containing Pirimiphos-methyl (97.8%) at a dose of 0.25 mg/kg for 56 days. Plasma and erythrocyte cholinesterase activities (ChEI) were measured twice prior to dosing, on days 1, 7, 14, 21, 28, 35, 42, 49 and 56 of dosing as well as on days 7, 14, 21 and 28 post-dosing (recovery period). Statistically significant decreases in plasma ChEI (up to 24%, relative to lowest and/or mean pre-dosing activity) were seen in three females between days 14 and 35. Plasma ChEI in males was slightly lower than pre-dosing, but generally within 10%. No effects were observed on erythrocyte ChE. The DER established the 0.25 mg/kg/day as a "threshold" NOEL based on marginal, transient decreases in plasma ChEI in the three females with the LOEL being >0.25 mg/kg/day. The Committee, however, determined that since only a single dose was tested and significant plasma ChEI was seen between days 14 and 35, this dose should be considered the LOEL rather than a "threshold" NOEL. **Therefore, the Committee recommended that the DER should be revised to reflect this change. (i.e., 0.25 mg/kg/day is the LOEL).**

Dose/Endpoint for establishing the RfD: LOEL = 0.25 mg/kg/day based on statistically significant decrease in plasm ChEI in three females between days 14 and 35.

Comments about Study and Endpoint: Since ChEI was seen at the only dose tested, the Committee considered this dose as the LOEL.

Uncertainty Factor (UF): 3000 (see discussion below).

$$\textbf{RfD} = \frac{\text{0.25 mg/kg/day (LOEL)}}{\text{3000 (UF)}} = \textbf{0.00008 mg/kg/day}$$

Chronic Dietary Risk Assessment Although, the developmental toxicity studies in rats and rabbits showed no increased sensitivity in fetuses as compared to maternal animals following in utero exposures and the two-generation reproduction toxicity study in rats showed no increased sensitivity in pups when compared to adults, the Committee determined that **the FQPA 10 x factor should be retained** because of the inadequate data base 1) to evaluate neurotoxicity following long-term exposure, 2) to assess the functional development of young animals and in turn the susceptibility to infants and children and 3) to determine the need for a developmental neurotoxicity study.

In addition to the 10 x for intra-species variation (for use of a human study) and 10 x for FQPA, the Committee also applied an additional 30 x Uncertainty Factor (UF) under FIFRA. The FIFRA UF includes a 3 x for the use of a LOEL and a 10 x for data gaps of a chronic toxicity study in dogs and a chronic toxicity/carcinogenicity study in rats as well as a delayed neurotoxicity study in hens. Thus, for chronic dietary risk assessment, an **UF of 3000 is required** and the RfD is revised as follows:

$$\textbf{Revised RfD} = \frac{\textbf{0.25 mg/kg/day (NOEL)}}{\textbf{3000 (UF)}} = \textbf{0.00008 mg/kg/day}$$

C. Occupational/Residential Exposure

1. Dermal Absorption

Dermal absorption studies are not available. Consequently, the Committee assumed dermal absorption factor of 100% (default value) for risk assessments. This assumption is supported by 1) the evidence of dermal absorption in the 21-day dermal toxicity where systemic toxicity was seen at the lowest dose tested and 2) the comparison of the LOELs of the oral and dermal toxicity studies based on the same endpoint (cholinesterase inhibition) in the same species (rabbits).

In the oral developmental toxicity in New Zealand White rabbits, the maternal LOEL was 24 mg/kg/day based on plasma and erythrocyte cholinesterase inhibition; the maternal NOEL was 12 mg/kg/day (MRID No. 43206301).

In the dermal toxicity study in New Zealand White rabbits, the LOEL was 4 mg/kg/day (LDT) based on red blood cell cholinesterase inhibition; a NOEL was not established (MRID No. 00129342).

Dermal Absorption Factor: 100% (default value).

2. Short-Term Dermal - (1-7 days)

Study Selected: 56-day Oral Toxicity - Human

MRID No. 00080732

Executive Summary: See Acute/Chronic Dietary

Dose and Endpoint for Risk Assessment: NOEL=0.25 mg/kg/day based on the lack of cholinesterase inhibition upto day 7.

Comments about Study and Endpoint: Since plasma or erythrocyte cholinesterase inhibition was not seen during days 1 through 7 (the exposure period of concern), this dose was considered to be the NOEL for this risk assessment (i.e., 1-7 days time period). The Committee did not utilize the results of the 21-day dermal toxicity in rabbits, because of the availability of adequate data in humans. Since an oral dose was identified, a dermal absorption rate of 100% should be used for dermal risk assessments.

This risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 56-day Oral Toxicity - Human

MRID No. 00080732

Executive Summary: See Acute/Chronic Dietary

Dose and Endpoint for Risk Assessment: LOEL=0.25 mg/kg/day based on significant plasma ChEI in three female subjects between days 14 and 35.

Comments about Study and Endpoint: Since plasma cholinesterase inhibition was seen between days 14 and 35, this dose was considered to be the LOEL for this risk assessment. The Committee did not utilize the results of the 21-day dermal toxicity in rabbits, because of the availability of adequate data in humans. Since an oral dose was identified, a dermal absorption rate of 100% should be used for dermal risk assessments.

This risk assessment is required.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: 56-day Oral Toxicity - Human

MRID No. 00080732

Executive Summary: See Acute/Chronic Dietary

Dose and Endpoint for Risk Assessment: LOEL=0.25 mg/kg/day based on significant plasma ChEI in three female subjects between days 14 and 35.

Comments about Study and Endpoint: Since plasma cholinesterase inhibition was seen between days 14 and 35, this dose was considered to be the LOEL for this risk assessment. The Committee did not utilize the 21-day dermal toxicity in rabbits, because of the availability of adequate data in humans. Since an oral dose was identified, a dermal absorption rate of 100% should be used for dermal risk assessments.

This risk assessment is required.

5. Inhalation Exposure (Any-Time period)

Except for an acute inhalation toxicity study, the results on which Pirimiphos-methyl is placed in Toxicity Category IV (LC_{50} = >5.04 mg/L), no other studies are available via this route. Therefore, the HIARC selected an oral dose for inhalation risk assessments. Inhalation risk assessments should be as follows:

Step I. The inhalation exposure component (i.e.,mg/L) using a 100% absorption rate (default value) should be converted to an equivalent oral dose (mg/kg/day)

Step II. The dermal exposure component (i.e., mg/kg/day) using a 100 % dermal absorption rate should be converted to an equivalent oral dose. This dose should then be combined with the converted oral dose in Step I.

Step III The combined dose from Step II should then be compared to the oral dose of 0.25 mg/kg/day to calculate the MOE's.

It should be noted, however, that the MOE requirements are different for the three time periods because of the use of this dose as a NOEL for Short-Term and as the LOEL for Intermediate-and Long-Term exposure (See Section. D).
This risk assessment is required.

D. Margin of Exposure for Occupational/Residential Exposures:

For **Short-Term dermal and inhalation** exposure risk assessments, **a MOE of 100 is required** and includes the conventional 10 x and the FQPA 10 x factors. For this time period, the oral dose is used as the NOEL because cholinesterase inhibition was *not seen* during the exposure period of concern (i.e., 1-7 days).

For **Intermediate-Term dermal and inhalation** exposure risk assessments, **a MOE of 300 is required** and includes the conventional 10 x and the FQPA 10 x as well as an additional 3 x factor under FIFRA. For this time period, the oral dose is used as the LOEL because cholinesterase inhibition *was seen* and thus requiring an additional 3 x factor under FIFRA (i.e., lack of a NOEL in the critical study).

For **Long-Term dermal and inhalation** exposure risk assessments, **a MOE of 3000 is required** and includes the conventional 10 x, the FQPA 10 x and an additional 30 x under FIFRA. The 30 x factor under FIFRA includes a 3 x for the use of a LOEL and a 10 x for data gaps of chronic toxicity studies in rats and dogs.

There are no registered residential uses in the current use pattern; however, the Committee determined that the FQPA is relevant for occupational exposure to Pirimiphos-methyl because of the concern for pregnant occupational workers exposed to this organophosphate chemical. The Committee determined that **the FQPA 10 x factor should be retained** because of the inadequate data base 1) to evaluate neurotoxicity following acute or long-term exposures, 2) to assess the functional development of young animals and in turn the susceptibility to infants and children and 3) to determine the need for a developmental neurotoxicity study. The data gaps are listed in Section IV.

E. Recommendation for Aggregate Exposure Risk Assessments

Not required since there are no registered residential uses and the use pattern does not indicate any exposure via drinking or ground water.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In a carcinogenicity study, groups of CD-1 mice (50/sex/dose) were fed diets containing Pirimiphos-methyl (89.8%) at dose levels of 0, 50, 200 or 400/300 ppm (0, 8.3, 33 or 52 mg/kg/day for males and 0, 9.7, 39 or 61 mg/kg/day for females, respectively) for 78 weeks. For chronic toxicity, the NOEL was 50 ppm (8.3 mg/kg/day) and the LOEL was 200 ppm (33 mg/kg/day) based on clinical signs (piloerection, hunched posture, dark eyes and hyperactivity) and decreased body weights. For cholinesterase inhibition the LOEL was 50 ppm (8.3 mg/kg/day; LDT) based on inhibition of plasma, red blood cell and brain cholinesterase activity; a NOEL was not established. The dose levels tested were judged to be adequate to assess the carcinogenic potential of Pirimiphos-methyl in male and female mice. **There was no evidence of carcinogenicity** (MRID No. 43968401).

In a combined chronic toxicity/carcinogenicity, groups of Wistar (SPF) rats (72/sex/dose) were fed diets containing Pirimiphos-methyl (purity not specified) at dose levels of 0, 10, 50 or 300 ppm (0, 0.4, 2.1 or 12.6 mg/kg/day, respectively) for 24 months. For chronic toxicity, the NOEL was 300 ppm (12.6 mg/kg/day, HDT) a LOEL was not established. This study, conducted in 1974, was classified as **Unacceptable** due to the deficiencies listed below: 1) lack of test article characterization; 2) data concentration and stability of diet mixes were not reported; 3) no rationale was provided for dose levels tested since no systemic toxicity was demonstrated at the highest dose level tested; 4) hematology, clinical chemistry and urinalysis parameters were not evaluated ; 5) individual animal data were not provided for evaluation of neoplastic and non-neoplastic findings; and 6) statistical analysis of data were not performed. **The Committee concurred with the classification of this study and concluded that a new study must be conducted to assess the carcinogenic potential of Pirimiphos-methyl in this species** (MRID No. 92147035).

The Committee concluded that the carcinogenic potential of Pirimiphos-methyl can not be determined due to the lack of an acceptable carcinogenicity study in rats.

IV. MUTAGENICITY

1. Gene Mutations

In a Salmonella typhimurium reverse gene mutation assay, independent trials were negative up to the highest concentration tested (5000 µg/plate) with or without metabolic (S9) activation (MRID No. 00144969).

In a mouse lymphoma TK $^{/-}$ forward gene mutation assay in independent trials performed using a microsuspension technique, negative results were obtained up to a concentration that was lethal in the absence of S9 activation and moderately cytotoxic in the presence of S9 activation (200 µg/mL). This dose was also the maximum soluble concentration that could be achieved in the aqueous tissue culture medium(MRID No. 41556303).

2. Chromosome Aberrations

An in vitro chromosome aberrations in human lymphocytes assay was negative up to cytotoxic concentrations (□116 µg/mL -S9; □289 µg/mL +S9)(MRID No. 41599501).

An in vivo bone marrow cytogenetic assay was negative in CD-1 male mice given single oral (gavage) doses ranging from 38-192 mg/kg (actual concentrations, based on analytical results) or exposed to 24-234 mg/kg/day (actual concentrations, based on analytical results) once daily for 5 consecutive days. Lethality and other clinical signs of toxicity were noted at the highest dose tested (HDT) in the multiple exposure dosing regimen. There was also suggestive evidence of bone marrow cytotoxicity at the HDT following multiple exposures(MRID No. 00126256).

3. Other Mutagenic Mechanisms

Positive results were obtained in an in vitro sister chromatid exchange (SCE) in Chinese hamster lung fibroblasts (Don cells) assay. Significant but not dose-related increases in the frequency of SCEs were obtained at 0.14-29 µg/mL without S9 activation. In the presence of S9 activation, the response was significant and dose-related at 14-145 µg/mL. Higher levels (□145 µg/mL +/-S9) were severely cytotoxic and mitotic delay was seen at □0.29 µg/mL -S9 and □2.9 µg/mL +S9(MRID No. 41599502.

4. Other Information:

In addition to the Acceptable studies, an Unacceptable and not upgradeable negative mouse dominant lethal assay (MRID No. 41556302) was submitted. Studies found in the open literature indicated that Pirimiphos-methyl was negative in the S. typhimurium reverse gene mutation assay and did not induce micronuclei in rat hepatocytes in vitro. Similarly, Rajini et al (1986) found no evidence of micronuclei induction in Swiss male mice administered oral doses of Pirimiphos-methyl up to 400 mg/kg once daily for 2 days. The HDT in this study was clearly cytotoxic to the target organ.

5.Conclusions:

The available studies submitted to the Agency in conjunction with the published data indicate that Pirimiphos-methyl is not mutagenic in bacteria or cultured mammalian cells. Pirimiphos-methyl did, however, induce SCE in vitro but was not clastogenic either in vitro or in vivo and was not genotoxic in primary rat hepatocytes. The data suggest, therefore, that the genotoxic activity demonstrated in the SCE assay is not expressed in vivo. Confidence in this conclusion is high since the suggestive evidence of test material interaction with the target cells noted in the submitted bone marrow cytogenetic assay was supported by the findings of Rajini et al (1986). Based on these considerations, the Committee concluded that there is no concern for mutagenicity at this time.

V. FQPA CONSIDERATIONS

1. Neurotoxicity Data

The Committee determined that the available studies are inadequate to assess the neurotoxic potential of Pirimiphos-methyl due to an existing data gap of an Acute Delayed Neurotoxicity Study in Hens (§81-7), Chronic Toxicity Study in Dogs (§83-1) and a Chronic Toxicity/Carcinogenicity Study in Rats (§83-5). These studies are discussed below:

Data gap exists for an acute delayed neurotoxicity study in hens. In a study available in the published literature, Johnson et al. 1990 did not observe delayed neurotoxicity following a single oral administration of Pirimiphos-methyl at a dose of 100 mg/kg followed by a second dose on day 21.

In an unacceptable subchronic delayed neurotoxicity study, groups of hens (10/sex/dose) received oral (gavage) administration of Pirimiphos-methyl (93.5%) at dose levels of 0.5, 1, 2.5, 5 or 10 mg/kg/day for a total of 90 doses. Two additional groups received 5 or 10 mg/kg/day for the same duration (90 doses) followed by a recovery period of 30 days. Control groups consisted of untreated control and vehicle control. The positive control group received Tri-ortho-cresyl-phosphate (TCOP) at 7.5 mg/kg/day. Treatment-related effects at 5 and 10 mg/kg/day included mortality 4/20 and 8/20, respectively), decrease in body weight and food consumption (10 mg/kg/day only), and a dose-related increase in the severity of clinical signs including quietness, weakness, sluggish movements, stumbling, leg stiffness, ruffled feathers, exaggerated leg movement, unsteadiness and wing drooping. At 10 mg/kg/day, clinical signs were seen even during the recovery period. Mild and less frequent signs were seen at 1 and 2.5 mg/kg/day dose groups. No effects were seen at 0.5 mg/kg/day. Histopathology revealed neuropathological changes (Grade III) in 1/6 hens from the non-recovery group that received continuous dosing; histopathology was not performed in hens in the recovery group. No NTE measurements were made. The NOEL was 5 mg/kg/day and the LOEL was 10 mg/kg/day based on positive histopathological lesions (MRID No. 00126254).

This study was classified as unacceptable because of intermittent dosing of some animals. At 10 mg/kg/day, the non-recovery group hens had less severe and less frequent signs of toxicity compared to those that were seen in recovery hens. At 10 mg/kg/day (non-recovery group) some hens that died earlier did not receive sufficient dosing and therefore, the histopathological examination did not reveal treatment-related effects.

In an acute neurotoxicity study in rats, groups of Sprague-Dawley rats (17/sex/dose) were given a single oral administration of Pirimiphos-methyl (89.8%) in corn oil at dose levels of 0, 15, 150 or 1500 mg/kg. Assessments were made for FOB and motor activity at pretest, 24 hours, 7 and 14 days after dosing. For cholinesterase inhibition, the LOEL was 15 mg/kg/day (LDT) based on significant decreases in plasma, red blood cell and brain cholinesterase activity; a NOEL was not established. For neurotoxicity, the LOEL was 1500 mg/kg/day based on clonic convulsions (in all rats) and related parameters (impaired mobility, decreased rearing, decreased rotarod performance, posture changes), ocular effects (alterations in pupil response, palpebral closure and exophthalmus), altered fur appearance, lacrimation and salivation, decreased grip strength and decreased body temperature; the NOEL was 15 mg/kg/day (MRID No. 43594101).

In a subchronic neurotoxicity study in rats, groups of Sprague-Dawley rats (10/sex/dose) were fed diets containing Pirimiphos-methyl (89.8%) at dose levels of 0, 3, 30 or 300 ppm (0, 0.2, 2.1 or 21.1 for males and 0, 0.2, 2.4 or 24.7 mg/kg/day for females, respectively) for 90-days. Assessments for FOB and motor activity and measurements of plasma, red blood cell and brain cholinesterase activity were made at pretest, and at weeks 3, 7 and 13 post treatment. No neurotoxicity or systemic toxicity was seen. The NOEL was 24.7 mg/kg/day (HDT); a LOEL was not established. For plasma ChEI, the NOEL was <0.2 mg/kg/day (LDT) and the LOEL was 0.2 mg/kg/day. For red blood cell ChEI, the threshold NOEL/LOEL was 2.1 mg/kg/day. For brain ChEI, the NOEL was 2.1 mg/kg/day and the LOEL was 21.1 mg/kg/day (MRID No. 43608201).

2. Determination of Susceptibility

There is no indication of additional sensitivity to young rats or rabbits following pre- and/or postnatal exposure to Pirimiphos-methyl in the developmental and reproductive toxicity studies.

(i) Developmental Toxicity:

In a prenatal developmental study, pregnant Alpk:AP (Wistar-derived) rats (24/dose) received oral (gavage) administration of Pirimiphos-methyl (88.5%) in corn oil at dose levels of 0, 1.5, 15 or 150 mg/kg/day during gestation days 7 through 16 of gestation. For maternal toxicity, the NOEL was 15 mg/kg/day and the LOEL was 150 mg/kg/day based on increased incidence of clinical signs characterized as abnormal gait, changes in behavior, irregular respiration, urinary incontinence and body tremors.. For developmental toxicity, the NOEL was ≥150 mg/kg/day (HDT); a LOEL was not established (MRID No. 00151623).

In a prenatal developmental toxicity study, pregnant New Zealand White rabbits received oral (gavage) administration of Pirimiphos-methyl (86.7%) in corn oil at dose levels of 0, 12, 24, or 48 mg/kg/day during gestation days 6 through 18. For maternal toxicity, the NOEL was 12 mg/kg/day and the LOEL was 24 mg/kg/day based on inhibition of plasma (37%) and red blood cell (44%) cholinesterase activity. For developmental toxicity, the NOEL was ≥ 48 mg/kg/day (HDT); a LOEL was not established (MRID No. 43206301).

(ii) Reproductive Toxicity:

In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing Primiphos- methyl (86.7%) at dose levels of 0, 10, 40 or 160 ppm (0, 0.87, 3.43 or 13.72 mg/kg/day for males and 0, 0.98, 3.88 or 15.41 mg/kg/day for females, respectively) during the premating period of 10 weeks (F_1 generation) and 12 weeks (F_2 generation). For parental systemic toxicity, the LOEL was 0.87 mg/kg/day in males and 0.98 mg/kg/day in females based on significant inhibition of plasma cholinesterase activity; a NOEL was not established. For offspring toxicity, the NOEL was 13.72 mg/kg/day in males and 15.4 mg/kg/day in females (HDT); a LOEL was not established (MRID No. 43726801).

3. Recommendation for a Developmental Neurotoxicity Study

Due to the existing data gaps of critical studies (listed below), the Committee was unable to determine whether or not a developmental neurotoxicity study would be required. Consequently, this data requirement was placed in a *reserve* status pending receipt of the following critical studies: an Acute Delayed Neurotoxicity study in hens, a Chronic Toxicity study in dogs and a Combined Chronic Toxicity/Carcinogenicity Study in rats. The following information was considered to support this decision:

(i) Evidence that support requiring a developmental neurotoxicity study:

- Pirimiphos-methyl is an organophosphate chemical that caused neurotoxicity via the oral and dermal routes characterized by clinical signs of neurotoxicity as well as inhibition of cholinesterase activities in mice, rats, rabbits, dogs and humans.
- Some evidence of delayed neurotoxicity was seen following repeated exposure to hens.
- The lack of acceptable chronic studies in rodents and non-rodents precludes an evaluation of the neurotoxic effects following long-term exposure to this chemical.

(ii) Evidence that do not support requiring a developmental neurotoxicity study:

- No evidence of abnormalities in the development of the fetal nervous system was observed in the developmental toxicity studies in rats and rabbits or in the pre/post natal reproduction study in rats.
- Neither brain weights nor histopathology (perfused/nonperfused) of the nervous system were affected in the acute and subchronic toxicity studies in rats.

4. Determination of Uncertainty Factor:

Although, the developmental toxicity studies in rats and rabbits showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures and the two-generation reproduction toxicity study in rats showed no increased sensitivity in pups when compared to adults, the Committee determined that **the FQPA 10 x factor should be retained because** of the inadequate data base 1) to evaluate neurotoxicity following acute and long-term exposure, 2) to assess the functional development of young animals and in turn the susceptibility to infants and children and 3) to assess the need for a developmental neurotoxicity study.

VI. DATA GAPS

1. Acute Delayed Neurotoxicity Study in Hens (§81-7)

2. Chronic Toxicity Study in Dogs (§83-1a)

3. Combined Chronic Toxicity/Carcinogenicity Study in Rats (§83-5)

VII SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected and Margins of Exposures for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE
Acute Dietary	NOEL =0.25	Lack of acute effects at the only dose tested.	28/56-day oral-Humans	100
Chronic Dietary	LOEL=0.25	Plasma cholinesterase inhibition.	56-day oral-Human	3000
Short-Term (Dermal)	Oral NOEL =0.25	Lack of effects up to day 7.	28/56-day oral-Humans	100
Intermediate-Term (Dermal)	Oral LOEL=0.25	Plasma cholinesterase inhibition.	28/56-day oral - Humans	300
Long-Term (Dermal)	Oral LOEL=0.25	Plasma cholinesterase inhibition.	28/56-day oral - Humans	3000
Short-Term (Inhalation)	Oral NOEL=0.25	Lack of effects up to day 7.	28/56-day oral - Humans	100
Intermediate-Term (Inhalation)	Oral LOEL=0.25	Plasma cholinesterase inhibition.	28/56-day oral - Humans	300
Long-Term (Inhalation)	Oral LOEL=0.25	Plasma cholinesterase inhibition.	28/56-day oral - Humans	3000

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Chemical:	**Pirimiphos-methyl (ANSI)**
PC Code:	***108102***
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Accession Number:	**412-01-0120**

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